Current Concepts in Autism

Symposium on the Special Needs Patient
American Association of Oral & Maxillofacial Surgeons
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Progress Comes From Participation

We wish to honor those individuals and families who have believed in research and been committed to participating again and again.

SAFARI Website:
Simons Foundation Autism Research Initiative

Autism Speaks: [www.autismspeaks.org](http://www.autismspeaks.org)
Prevalence

Current Estimates:

- Overall in children: 1/100
- Boys: 1/87   Girls: 1/110
- Adults: 1/100

Dramatic increase is related to general appreciation of the 50% who are verbal and without intellectual disability.
Recurrence Rate

- One child with autism in family: 20%
- More than one child with autism: 37%
Every person who talks about the cause of autism, its treatment or its diagnosis and course needs to have an accurate grasp of the findings at all levels from gene to behavior.

Also implies a responsibility to be active listeners and learners in order to seam the pieces together.
The Responsibility & Challenge

Everyone Who Talks About Cause Needs to Know Scientific Evidence & Principles
  Need fewer “nice stories”
  Need to rely on science
Communicate: Families & public want to know
  Vacuums are dangerous
Integration of knowledge informs each level & maximally improves treatment
What does ‘cause’ mean?

- Etiology
- Pathophysiology
- Functional analysis of behavior
Spontaneous Mutations: Increased rate of "de novo" copy number variations: submicroscopic deletions or duplications of DNA sequences. More common in simplex than multiplex families. Opened door to two genetic mechanisms: inherited gene mutations and spontaneous copy number mutations.

Potential reversal of Neurodevelopmental Disorders (in Fragile X, Rett & Angelman Syndromes) in adult mice.

Abnormalities in Genetic Code for Brain Development

Abnormal Mechanisms of Brain Development

Structural and Functional Abnormalities of Brain

Cognitive & Neurological Abnormalities

Behavioral Syndrome
Etiologies

- Syndromic autism: ~20% of cases
  cases with recognizable genetic syndrome

- Non-syndromic or idiopathic autism:
  cases without a recognizable syndrome
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene(s) associated with the syndrome</th>
<th>Proportion of patients with the syndrome that have an ASD</th>
<th>Proportion of patients with an ASD that have the syndrome</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>15q duplication — Angelman syndrome</td>
<td>UBE3A (and others)</td>
<td>&gt;40%</td>
<td>1–2%</td>
<td>101–103</td>
</tr>
<tr>
<td>16p11 deletion</td>
<td>Unknown</td>
<td>High</td>
<td>~1%</td>
<td>20, 35, 44</td>
</tr>
<tr>
<td>22q deletion</td>
<td>SHANK3</td>
<td>High</td>
<td>~1%</td>
<td>21, 22, 104</td>
</tr>
<tr>
<td>Cortical dysplasia-focal epilepsy syndrome</td>
<td>CNTNAP2</td>
<td>~70%</td>
<td>Rare</td>
<td>37</td>
</tr>
<tr>
<td>Fragile X syndrome</td>
<td>FMR1</td>
<td>25% of males; 6% of females</td>
<td>1–2%</td>
<td>105</td>
</tr>
<tr>
<td>Joubert syndrome</td>
<td>Several loci</td>
<td>25%</td>
<td>Rare</td>
<td>106</td>
</tr>
<tr>
<td>Potocki–Lupski syndrome</td>
<td>Chromosome position 17p11</td>
<td>~90%</td>
<td>Unknown</td>
<td>107</td>
</tr>
<tr>
<td>Smith–Lemli–Opitz syndrome</td>
<td>DHCR7</td>
<td>50%</td>
<td>Rare</td>
<td>108</td>
</tr>
<tr>
<td>Rett syndrome</td>
<td>MECP2</td>
<td>All individuals have Rett syndrome</td>
<td>~0.5%</td>
<td>109</td>
</tr>
<tr>
<td>Timothy syndrome</td>
<td>CACNA1C</td>
<td>60–80%</td>
<td>Unknown</td>
<td>24</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>TSC1 and TSC2</td>
<td>20%</td>
<td>~1%</td>
<td>110</td>
</tr>
</tbody>
</table>

The rates quoted in the table depend on the population that is being evaluated. For example, rates are higher in individuals from simplex families compared with multiplex families, and are higher in dysmorphic and mental retardation populations compared with idiopathic populations. ‘High’ is used for syndromes in which no good estimates exist (that is, only a handful of individuals with the syndrome in question have been identified). It should also be noted that none of the studies cited here indicates that assessment for the autism spectrum disorder (ASD) was performed blind to a patient’s primary diagnosis. An expanded version of the table with additional variables can be found in Supplementary information S1 (table). CACNA1C, calcium channel voltage-dependent L type alpha 1C subunit; CNTNAP2, contactin associated protein-like 2; DHCR7, 7-dehydrocholesterol reductase; FMR1, fragile X mental retardation 1; MECP2, methyl CpG binding protein 2; SHANK3, SH3 and multiple ankyrin repeat domains 3; TSC1, tuberous sclerosis 1; TSC2, tuberous sclerosis 2; UBE3A, ubiquitin protein ligase E3A.
Most Common Known Etiologies

- Tuberous sclerosis
- Chromosome 15 microduplications
- 16p, 22q microdeletions
- Fragile-X syndrome

Biggest news: copy number variations provide new genetic mechanism esp. in non-familial cases
Microarray genetic analysis is now recommended as standard part of assessment
### Evidence scores for ASD gene candidates

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome or mutation(s)</th>
<th>Replicated association</th>
<th>Analysis of variant</th>
<th>Mouse model</th>
<th>Other evidence</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVPR1A</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>DISC1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>ITGB3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>AHI1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>EN2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>GRIK2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1; homozygous mutation results in non-syndromic mental retardation</td>
<td>2</td>
</tr>
<tr>
<td>NRXN1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
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<tr>
<td>SLC25A12</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1; associated with neurite outgrowth, expression is upregulated in ASD brain</td>
<td>2</td>
</tr>
<tr>
<td>Promising</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CACNA1C</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>CNTNAP2</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>MET</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1; expression reduced in brains of cases versus controls</td>
<td>3</td>
</tr>
<tr>
<td>OXTR</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1; expression reduced in blood of cases versus controls</td>
<td>3</td>
</tr>
<tr>
<td>SHANK3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1; modulates glutamate-dependent reconfiguration of dendritic spines</td>
<td>3</td>
</tr>
<tr>
<td>SLC6A4</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1; clinical benefit from inhibitors, variation linked to gray-matter volume</td>
<td>3</td>
</tr>
<tr>
<td>CADPS2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>DHCR7</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1; hypocholesterolaemia in a proportion of probands</td>
<td>4</td>
</tr>
<tr>
<td>FMR1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>NLGN3</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>NLGN4X</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>PTEN</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1; regulates dendrite morphology and function of glutamatergic synapses</td>
<td>4</td>
</tr>
<tr>
<td>TSC2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1; expression is dysregulated in pervasive developmental disorders</td>
<td>4</td>
</tr>
<tr>
<td>GABRB3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1; expression is dysregulated in pervasive developmental disorders</td>
<td>5</td>
</tr>
<tr>
<td>MECP2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1; MECP2 deficiency causes reduced expression of UBE3A and GABRB3</td>
<td>5</td>
</tr>
<tr>
<td>TSC1</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1; regulates dendrite morphology and function of glutamatergic synapses</td>
<td>5</td>
</tr>
<tr>
<td>UBE3A</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1; expression is dysregulated in pervasive developmental disorders</td>
<td>5</td>
</tr>
<tr>
<td>RELN</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1; levels reduced in brains of cases versus controls</td>
<td>6</td>
</tr>
<tr>
<td>Probable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The currently predominate genetic model of the pathogenesis of ASD focuses on abnormal formation and/or maintenance of synaptic connections. This model has been suggested by the identification of genes, e.g. NLGN3, CNTN4, NRXN1, CNTNAP2, and SHANK3 in candidate loci. These are all synaptic cell adhesion molecules (or CAMs) which are crucial for the initial contact between pre- and postsynaptic neurons and serve to maintain cell adhesion and to assemble/anchor synaptic scaffolding proteins. However, another model is suggested by the genetic data and focuses on the developmental neurobiological processes of neuronal axon outgrowth and targeting. This is suggested by the identification of several members of the Leucine rich repeat (LRR) family (e.g. SLIT1, AMIGO1, LRRN3, LRRTM3), multiple mediators of axonal microtubule stabilization (tau kinases), as well as genes coding for classic axonal pathfinding molecules (e.g. various Semaphorins and Ephs) as potential candidate genes. Additionally, as we learn more about the functions of synaptic CAMs during development, we often find they have neuritic outgrowth and guidance functions before the synapse is formed (e.g. SYNGAP1).
1. Genes whose products affect **axonal targeting and pathfinding** i.e. getting neurons connected in the right way

**Cadherins and leucine-rich repeat proteins** which are cell surface proteins expressed in neuronal processes - thought to be important for establishing connections between cells in the developing brain
2. Those that affect synaptic functioning:

Neurexins and neuroligins bind each other across the synapse (i.e. glue neurons together) and mediate signaling across the synapse, and affect the properties of neural networks by specifying synaptic functions (i.e. excitatory versus inhibitory)
3. Those that appear to affect *dendritic function*:

*Shank* family of synaptic proteins function as molecular scaffolds at the post synaptic density and promote the maturation and enlargement of dendritic spines.
Defining molecular mechanisms empowers a new world of interventions

mTor inhibitor Rapamycin to prevent development of seizures, intellectual disability and ASD in infants and toddlers diagnosed with TSC gene tuberous sclerosis; clinical trials in progress

Fra-X medication in trial also
News About Pathophysiology
Cognitive & Neurological Profile

- Selective impairments in higher order abilities across domains
- Greatest manifestations in domains with highest information integration demands
- With intact or enhanced elementary abilities

Practical Implications:
- Information processing disorder - reduced comprehension
- Deficit in implicit learning and categorization - automatic
- Rely on visual system even when stimulus is language
The Profile of Intact & Impaired Abilities in High Functioning Autistic Individuals

<table>
<thead>
<tr>
<th>Intact or Enhanced</th>
<th>Cognitive Weaknesses</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Attention</td>
<td>• Complex Sensory</td>
</tr>
<tr>
<td>• Sensory Perception</td>
<td>• Complex Motor</td>
</tr>
<tr>
<td>• Elementary Motor</td>
<td>• Complex Memory</td>
</tr>
<tr>
<td>• Simple Memory</td>
<td>• Complex Language</td>
</tr>
<tr>
<td>• Formal Language</td>
<td>• Concept-formation</td>
</tr>
<tr>
<td>• Rule-learning</td>
<td>• Face Recognition</td>
</tr>
<tr>
<td>• Visuospatial processing</td>
<td></td>
</tr>
</tbody>
</table>
Brain Function & Structure: Connectivity & Integration
fMRI Activation During a Spatial Working Memory Task  (Courtesy John Sweeney)
Reliably lower functional connectivity for autism participants between pairs of key areas during sentence comprehension (red end of scale denotes lower connectivity)
Reliable differences in functional connectivity: autism group has lower functional connectivity but same rank order.
New Findings New View

- Increase in HC & total brain volume
- Stunted dendritic tree development CA1
- Widespread cortical functional underconnectivity
- Gene abnormalities - many & scattered across genome; all coding for development of connections among neurons
Figure 2. Occipital–frontal (OFC) Z score measurements ($N = 195$) with mean estimated growth trajectory for 28 children with autism spectrum disorder (hierarchical linear model two-piece linear model centered at 12 months).
Began with: home video movies showed symptoms of autism long before diagnosis

Key Q: What are the first behavioral characteristics that predict the development of autism?

Method: study of infants with an older sibling diagnosed with autism—"infant sibs"
Developmental Characteristics of Infant Sibs:
Visual Regard-Sensory-Repetitive Signs

- Unusual visual regard at 12 mos
- Repetitive waving of arms and hands at 12 mos
- Sensory-related behaviors: under and over responsiveness at 12 months
- Social emotional: no temperamental differences at 6 mos, over time temperamentally more difficult with more intense distress and more time fixating on objects; accompany- don’t predate- sx
Delays in verbal and nonverbal language at 12 months but not earlier

Developmental differences at 12 mos on standardized tests- a developmental deceleration

Gap widens between 12 & 24 months and beyond

At 24 months, emotional and behavioral dysregulation distinguished infant sibs dx ASD
Onset: not early or regressive but rather slower or faster mounting of symptoms - a deceleration of development: core symptoms present at 12 mos and grow more severe over time.

“Associated symptoms” are integral - irritability, sensory responsivity, activity level, poor gross motor development.
“These findings do not support the view that autism is primarily a social-communicative disorder and instead suggest that autism disrupts multiple aspects of development rather simultaneously.”

“Children’s developmental rates are decelerating markedly in a 12 month period, with IQs dropping from average to below 50 for some children.”

Sally Rogers, 2009
Tip Offs to ASD in Child or Adult

- Seem odd or strange (social impairment)
- Unusual memory for trivial details or facts
- Unusual interests- obsessions or preoccupations
- Poor common sense and problem solving
- Difficulty comprehending what you say
- Little face expression
- Monotone or odd voice- often very loud
- Clumsy
What does it mean to you?

- Step back - increase social distance; listen & watch
- Stop the social chatter
- Say what you have to say in a few words
- Pause to allow time for processing
- Show and use visuals before acting (social stories)
- Ask if the person is ready to proceed - wait for the answer
- Use the same room, words and procedures for every visit; watch HBO movie “Temple Grandin”
Other Tips For Success

- Have practice visits (tours, wandering, watching)
- Practice should include looking at room, equipment, and hearing sounds
- Agree on a signal to stop and to rest- and obey it
- Make them the first appointment
- Have a quiet waiting place (no music or tv)
- Listen to mom’s advice again and again
- Listen to what they say, not how they say it- think what it means about what they need from you
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